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USPT,PGPB,JPAB,EPAB,DWPI	l20 and angiotensin	0	L31
USPT,PGPB,JPAB,EPAB,DWPI	l28 and cre	318	L30
USPT,PGPB,JPAB,EPAB,DWPI	l28 with cre	0	L29
USPT,PGPB,JPAB,EPAB,DWPI	((435/455 |435/463 |435/320.1 |435/325)!.CCLS.)	11990	L28
USPT,PGPB,JPAB,EPAB,DWPI	l23 with angiotensin	0	L27
USPT,PGPB,JPAB,EPAB,DWPI	l23 with loxp	0	L26
USPT,PGPB,JPAB,EPAB,DWPI	l23 with cre	0	L25
USPT,PGPB,JPAB,EPAB,DWPI	l23 with (recombinase)	0	L24
USPT,PGPB,JPAB,EPAB,DWPI	((800/18 |800/21 |800/22 |800/25 |800/3)!.CCLS.)	363	L23
USPT,PGPB,JPAB,EPAB,DWPI	l20 with cre	0	L22
USPT,PGPB,JPAB,EPAB,DWPI	l20 with recombinase	0	L21
USPT,PGPB,JPAB,EPAB,DWPI	capecchi-m$.in.	20	L20
USPT,PGPB,JPAB,EPAB,DWPI	l18 with cre	0	L19
USPT,PGPB,JPAB,EPAB,DWPI	greer-j.in.	25	L18
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USPT,PGPB,JPAB,EPAB,DWPI	l14 with cre	0	L15
USPT,PGPB,JPAB,EPAB,DWPI	bernstein-k$.in.	65	L14
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USPT,PGPB,JPAB,EPAB,DWPI	l10 with l7	0	L11
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USPT,PGPB,JPAB,EPAB,DWPI	l7 with excis$	5	L9
USPT,PGPB,JPAB,EPAB,DWPI	l7 with angiotensin	0	L8
USPT,PGPB,JPAB,EPAB,DWPI	l6 with (gene therapy)	82	L7
USPT,PGPB,JPAB,EPAB,DWPI	l1 with transgen$	151	L6
USPT,PGPB,JPAB,EPAB,DWPI	l1 and tACE	1	L5
USPT,PGPB,JPAB,EPAB,DWPI	l1 and l2	0	L4
USPT,PGPB,JPAB,EPAB,DWPI	angiotensin	9344	L3
USPT,PGPB,JPAB,EPAB,DWPI	angiotensin with l1	0	L2
USPT,PGPB,JPAB,EPAB,DWPI	cre	1688	L1

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L2 11929 CRE

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L3 160055 TRANSGEN?

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L4 1391 L2 AND L3

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L5 61 L4 AND (GENE THERAPY)

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PROCESSING COMPLETED FOR L5
L6 38 DUP REM L5 (23 DUPLICATES REMOVED)

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L6 ANSWER 1 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:338738 CAPLUS
DOCUMENT NUMBER: 134:348961
TITLE: Site-specific **transgene** integration mediated by a hybrid adenovirus/adeno-associated virus vector using the **Cre**/loxP-expression-switching system
INVENTOR(S): Ueno, Takashi; Matsumura, Hajime; Tanaka, Keiji; Iwasaki, Tomoko; Ueno, Mitsuhiro; Fujinaga, Kei; Asada, Kiyozo; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Shuzo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032899	A1	20010510	WO 2000-JP7373	20001023

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: JP 1999-308839 A 19991029
AB A method of transferring a **transgene** into cells, involving the step of transferring into the cells using an adenovirus vector, a first nucleic acid having a sequence adeno-assocd. virus-origin inverted terminal repeats (ITRs) on both sides of the target **transgene** to be transferred, and a second nucleic acid having an adeno-assocd. virus-origin rep gene and a promoter for expressing this gene and further carrying a stuffer sequence inserted thereinto sandwiched between two recombinase recognition sequences and located between the rep gene and the promoter; and the step of expressing the Rep protein under the action of recombinase in the cells obtained in the above step to thereby integrate the target foreign gene into the chromosomal DNA, is disclosed. As vectors, adenoviruses (Ads) have many attractive advantages for in vivo **gene therapy**. However, Ads do not usually integrate into the host genome and gene expression is, thus, transient. Adeno-assocd. virus (AAV) integrates into a specific locus (AAVS1) on the human host's chromosome 19, while conventional recombinant AAV (rAAV) vectors do not possess this property because such vectors lack the rep gene. AAV vectors carrying the rep gene do not have enough space for insertion of a **transgene**. The authors have constructed hybrid adenovirus/adeno-assocd. virus (Ad/AAV) vectors which has the advantages of both Ads and AAVs for gene transfection. Given that the rep gene products inhibit propagation of Ads, the authors used the **Cre**/loxP-expression-switching system to regulate the expression of the rep gene. In this study, we report the development of three helper-dependent adenoviral (HD) vectors, one carrying the Rep78 gene, the other an AAV-ITR-flanked **transgene**, and the third for expression of **Cre** recombinase gene. The Ad/AAV vectors easily propagate, can efficiently infect a broad range of cell types, and can integrate into a specific locus on host chromosomes.
REFERENCE COUNT: 3
REFERENCE(S): (1) Alessandra, R; Proc Natl Acad Sci USA 1999, V96, P2615
(2) Takashi, U; Biochemical and Biophysical Reserch Communications 2000, V273(2), P473
(3) Yoji, O; Journal of General Virology 1999, V80, P2477

L6 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CAPLUS
DOCUMENT NUMBER: 134:81749
TITLE: Method for deleting a nucleic acid sequence in a specified tissue from a DNA introduced into the organism
INVENTOR(S): Thomas, Kirk R.; Bernstein, Kenneth E.; Bunting, Michaeline; Greer, Joy; Capecchi, Mario
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000809	A1	20010104	WO 2000-US17828	20000629

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-141267 P 19990630
AB The present invention is directed to a method for deleting DNA sequences in a tissue specific manner. In one embodiment, DNA sequences are specifically deleted in germline tissue. In a second embodiment, DNA sequences are specifically deleted in desired somatic tissue. The present invention is further directed to a nucleic acid mol. for use in the method. More specifically, a nucleic acid mol. is provided by the present invention which comprises (a) a recombinase site, (b) a tissue-specific promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a recombinase site. The nucleic acid mol. may further comprise a gene which is desired to be incorporated into and expressed in a **transgenic** organism. The method can be used in both plants and animals, and has many applications as described herein.
REFERENCE COUNT: 1
REFERENCE(S): (1) Kitamoto; Biochemical and Biophysical Research Communications 1996, V222(3), P742 CAPLUS

L6 ANSWER 3 OF 38 MEDLINE
ACCESSION NUMBER: 2001285479 MEDLINE
DOCUMENT NUMBER: 21102048 PubMed ID: 11157990
TITLE: An inducible mouse model for epidermolysis bullosa simplex: implications for **gene therapy**.
AUTHOR: Cao T; Longley M A; Wang X J; Roop D R
CORPORATE SOURCE: Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
CONTRACT NUMBER: AR62228 (NIAMS)
SOURCE: JOURNAL OF CELL BIOLOGY, (2001 Feb 5) 152 (3) 651-6.
Journal code: HMV; 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered PubMed: 20010222
Entered Medline: 20010524
AB The Dowling-Meara variant of epidermolysis bullosa simplex (EBS-DM) is a severe blistering disease inherited in an autosomal-dominant fashion. Here we report the generation of a mouse model that allows focal activation of a mutant keratin 14 allele in epidermal stem cells upon topical administration of an inducer, resulting in EBS phenotypes in treated areas. Using laser capture microdissection, we show that induced blisters healed by migration of surrounding nonphenotypic stem cells into the wound bed. This observation provides an explanation for the lack of mosaic forms of EBS-DM. In addition, we show that decreased mutant keratin 14 expression resulted in normal morphology and functions of the skin. Our results have important implications for **gene therapy** of EBS and other dominantly inherited diseases.

L6 ANSWER 4 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2001170661 EMBASE
TITLE: Interruption of coding sequences by heterologous introns can enhance the functional expression of recombinant genes.
AUTHOR: Lacy-Hulbert A.; Thomas R.; Li X.-P.; Lilley C.E.; Coffin R.S.; Roes J.
CORPORATE SOURCE: J. Roes, Department of Medicine, Windeyer Institute of Medical Sci., University College London, 46 Cleveland Street, London W1P 6DB, United Kingdom
SOURCE: Gene Therapy, (2001) 8/8 (649-653).
Refs: 18
ISSN: 0969-7128 CODEN: GETHEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Sustained expression of recombinant proteins is a critical factor for the effectiveness of numerous applications in the biomedical sciences including the treatment of human disease by **gene therapy**, the large scale production of therapeutic proteins, as well as the investigation of gene function by **transgenesis** or cell type specific mutagenesis. Although much attention has been paid to the optimisation of regulatory sequences such as promoters, untranslated regions and polyadenylation signals, effective and sustained expression of recombinant genes in vivo is often difficult to achieve. Here we report that the creation of artificial exons, by insertion of two short heterologous introns into open reading frames, is not only compatible with functional expression, but also leads to a 30-fold enhancement of mRNA production for both green fluorescent protein and the bacteriophage P1-derived **Cre** recombinase. The levels of green fluorescence were increased five-fold in cell lines and sustained long-term expression at increased levels was observed in rat brain after transduction with a herpes simplex virus-based vector. The data presented identify a means by which the expression of recombinant genes can be enhanced considerably, in addition to and independently from the surrounding regulatory sequences. The method should help obtain sustained and effective expression of recombinant proteins in vivo.

L6 ANSWER 5 OF 38 MEDLINE
ACCESSION NUMBER: 2001285478 MEDLINE
DOCUMENT NUMBER: 21102047 PubMed ID: 11157989
TITLE: Focal activation of a mutant allele defines the role of stem cells in mosaic skin disorders.
AUTHOR: Arin M J; Longley M A; Wang X J; Roop D R
CORPORATE SOURCE: Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
CONTRACT NUMBER: HD25479 (NICHD)
SOURCE: JOURNAL OF CELL BIOLOGY, (2001 Feb 5) 152 (3) 645-9.
Journal code: HMV; 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered PubMed: 20010222
Entered Medline: 20010524
AB Stem cells are crucial for the formation and maintenance of tissues and organs. The role of stem cells in the pathogenesis of mosaic skin disorders remains unclear. To study the molecular and cellular basis of

mosaicism, we established a mouse model for the autosomal-dominant skin
blistering disorder, epidermolytic hyperkeratosis (MIM 113800), which is caused by mutations in either keratin K1 or K10. This genetic model allows
activation of a somatic K10 mutation in epidermal stem cells in a spatially and temporally controlled manner using an inducible Cre recombinase. Our results indicate that lack of selective pressure against certain mutations in epidermal stem cells leads to mosaic phenotypes. This
finding has important implications for the development of new strategies for somatic gene therapy of dominant genodermatoses.

L6 ANSWER 6 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
DUPLICATE 2
ACCESSION NUMBER: 2001:226197 BIOSIS
DOCUMENT NUMBER: PREV200100226197
TITLE: System for efficient helper-dependent minimal adenovirus construction and rescue.
AUTHOR(S): Hillgenberg, Moritz (1); Schnieders, Frank; Loeser, Peter;
Strauss, Michael
CORPORATE SOURCE: (1) DevelopGen AG, Robert-Roessle-Str. 10, D-13125,
Berlin-Buch: mhillgenberg@hepavec.com Germany
SOURCE: Human Gene Therapy, (April 10, 2001) Vol. 12, No. 6, pp.
643-657. print.
ISSN: 1043-0342.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Helper-dependent minimal adenoviral vectors deleted for all viral coding
sequences are promising vectors for gene therapy. They retain only the adenovirus cis elements for replication and packaging, can
accommodate up to 36 kb of foreign DNA, and exhibit prolonged transgene expression and reduced tissue toxicity as compared with first-generation adenoviral vectors. We have developed a system consisting
of a set of cosmid cloning vectors (pMV and pMVX) for simple routine construction and efficient rescue of minimal adenoviral vectors. In the cloning vectors the inverted terminal repeats (ITRs) are flanked by recognition sites for the super rare-cutting endonuclease I-SceI. This allows the release of linear minimal adenovirus genomes for rescue of minimal adenovirus regardless of the sequence of the insert DNA. pMVX
contains a multiple cloning site for the insertion of 26 to 36 kb of therapeutic DNA. pMVX contains a noncoding human X-chromosomal DNA
fragment as a vector backbone, which provides endonuclease restriction sites that allow for complete or partial replacement of the vector backbone by 1 to 26 kb of therapeutic DNA sequences, while retaining a packageable final minimal adenovirus genome size between 27 and 37.5 kb.
Both vectors exist in two forms, with or without an Escherichia coli lacZ reporter gene cassette. Several minimal adenoviral vectors with insert sizes ranging from 1.5 to 16 kb were constructed with these cloning vectors. Minimal adenoviruses were efficiently rescued and amplified to high titers, using a Cre/lox-based helper system. Vectors containing the X-chromosomal backbone were stable during amplification.
This simple and efficient system facilitates the construction of minimal adenoviruses and should be useful for further improvement of these new
vectors.

L6 ANSWER 7 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:209835 BIOSIS
DOCUMENT NUMBER: PREV200100209835
TITLE: Are we creating problems? Negative effects of Cre recombinase.
AUTHOR(S): Adams, David J. (1); van der Weyden, Louise
CORPORATE SOURCE: (1) Basic and Clinical Genomics Laboratory, Department of
Physiology, Institute for Biomedical Research, University of Sydney, Sydney, NSW, 2006: dadams@physiol.usyd.edu.au
Australia
SOURCE: Genesis The Journal of Genetics and Development, (March,
2001) Vol. 29, No. 3, pp. 115. print.
ISSN: 1526-954X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L6 ANSWER 8 OF 38 MEDLINE
ACCESSION NUMBER: 2001167453 MEDLINE
DOCUMENT NUMBER: 21165824 PubMed ID: 11269336
TITLE: Stabilization of transgenes delivered by recombinant adenovirus vectors through extrachromosomal replication.
AUTHOR: Krougliak V A; Krougliak N; Eisensmith R C
CORPORATE SOURCE: Institute for Gene Therapy and Molecular Medicine, Mount
Sinai School of Medicine, New York, NY 10029, USA.. krougv01@doc.mssm.edu
CONTRACT NUMBER: DK51700 (NIDDK)
DK53333 (NIDDK)
SOURCE: JOURNAL OF GENE MEDICINE, (2001 Jan-Feb) 3 (1) 51-8.
Journal code: DLU; 9815764. ISSN: 1099-498X.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered PubMed: 20010327
Entered Medline: 20010517
AB BACKGROUND: A major limitation of adenovirus-mediated gene therapy for metabolic and inherited diseases is the instability of transgene expression in vivo. This instability results, at least in part, from the inability of the vector genome to maintain the transgene through replication or integration. In this study we evaluated the possibility of stabilization of an adenovirus-delivered transgene by non-adenovirus replicative elements. METHODS: We have
developed a novel system for the maintenance of transgenes delivered by adenovirus vectors through extrachromosomal replication. In
its initial configuration, this system combines the Epstein-Barr virus (EBV) replicative elements, a tetracycline (Tc)-inducible expression system, and the Cre-lox recombination system in the context of a single E1/E3/E4-deleted adenovirus vector. Induction of Cre expression initiates a Cre-mediated recombination, resulting in the excision of a fragment of the vector genome and its circularization into an EBV-based episome. RESULTS: In vitro studies have demonstrated
that excision of the circular episome can occur in a cell-free system as well as in cultured cells transfected with plasmid DNA or transduced by a
virus vector carrying the episome-excising cassette. PCR studies have shown that in proliferating, non-permissive, cultured primate cells the episome generated from the adenovirus vector is maintained much more
stably than the genome of the parent vector. This episome was also able to
replicate in mammalian cells. CONCLUSION: Together these studies demonstrate the feasibility of this approach for the stabilization of transgenes delivered to dividing cells by adenovirus vectors.

L6 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:756892 CAPLUS
DOCUMENT NUMBER: 133:318280
TITLE: Use of retrovirus vectors and the cre/lox system to achieve efficient, stable, site-specific integration of transforming DNA
INVENTOR(S): Bouhassira, Eric; Leboulch, Philippe
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA; Albert
Einstein College of Medicine of Yeshiva University
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000063410	A1	20001026	WO 2000-US9782	20000412

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-293303 A1 19990416
AB Methods and compns. for transforming cells, resulting in efficient and stable site-specific integration of **transgenes**, are disclosed. Transformation is achieved by introducing into a cell an acceptor vector, preferably a retroviral vector, that integrates into the genome of the cell. The acceptor vector comprises two inverted (incompatible) lox sequences, L1 and L2, that differ by a few bases and that cannot recombine with one another. Prior to recombination, the acceptor DNA is preferably integrated into the genome of a cell, such as an embryonic stem cell or a fertilized egg. The acceptor DNA optionally may further contain a neg. selectable marker to allow for screening of cells which have undergone the desired site-specific recombination (e.g., DNA cassette exchange). A donor vector carrying a **transgene** flanked by the same L1 and L2 sequences and a pos. selectable marker is then introduced into the transformed cells. Stable gene transfer is initiated by **cre** recombinase-mediated recombination of the lox L1 and L2 sequences. A retrovirus is used for the first transformation because of its site-specific integration. Any suitable vector, such as an adeno-assocd. virus, may be used for the second transformation.
REFERENCE COUNT: 5
REFERENCE(S): (1) Ass Pour Le Dev de La Rech En; FR 2745008 A 1997
CAPLUS
(2) Bouhassira, E; BLOOD 1997, V90(9), P3332 CAPLUS
(3) Einstein Coll Med; WO 9747758 A 1997 CAPLUS
(4) Feng, Y; JOURNAL OF MOLECULAR BIOLOGY 1999, V292(4), P779 CAPLUS
(5) Genvec Inc; WO 9709439 A 1997 CAPLUS

L6 ANSWER 10 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:756843 CAPLUS
DOCUMENT NUMBER: 133:318273
TITLE: Increased gene expression due to heterologous intron for use in **gene therapy** or in obtaining stress resistant **transgenic** plants
INVENTOR(S): Roes, Jurgen Theodor
PATENT ASSIGNEE(S): University College London, UK
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000063359	A2	20001026	WO 2000-GB1454	20000417
WO 2000063359	A3	20010222		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: GB 1999-8788 A 19990416
AB A polynucleotide comprising a coding sequence, which coding sequence comprises a heterologous intron, for use in a method of treatment of the human or animal body by therapy. The intron may be obtain from the mouse or human Ig Ig-C.mu. or Ig-C.epsilon. genes. A cell, animal or plant comprising the polynucleotide and methods of making such cells, animals or plants are also provided.

L6 ANSWER 11 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:592852 CAPLUS
DOCUMENT NUMBER: 133:173055
TITLE: Helper dependent adenovirus vectors based on site-specific recombinases
INVENTOR(S): Graham, Frank L.; Anton, Martina; Rudnicki, Michael A.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000049168	A2	20000824	WO 2000-US3807	20000215
WO 2000049168	A3	20010301		

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1999-251955 A 19990217
US 1999-351819 A 19990713
AB This invention provides helper-dependent adenovirus cloning vectors and helper adenoviruses, and methods for making and using such prepns., wherein the helper adenoviruses contain recombinase target sites that are useful in reducing the level of contamination of helper virus in helper-dependent adenovirus vector prepns. The invention is exemplified using an adenovirus vector with a deletion of all viral coding sequence for the expression of a leptin gene and its non-packageable helper adenovirus where its packaging signals within E1 region are flanked on both sides by site-specific recombinase recognition sites, such as lox sites, or FRT sites, or both. Upon the viral infection of the cells expressing high level site-specific recombinase, such as Cre or FLP or both, the packaging signals in helper virus are excised and the helper adenovirus genome is not packaged.

L6 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:592850 CAPLUS
DOCUMENT NUMBER: 133:173054
TITLE: A system for production of helper dependent adenovirus vectors based on use of endonucleases
INVENTOR(S): Graham, Frank L.; Ng, Philip; Parks, Robin; Bacchetti, Silvia; Anglana, Mauro
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000049166	A2	20000824	WO 2000-US3771	20000215
WO 2000049166	A3	20010412		

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1999-250929 A 19990218
US 1999-475813 A 19991230
AB The present invention relates to methods for efficient and reliable construction of adenovirus vectors which contain and express foreign DNA and are useful for gene transfer into mammalian cells, for vaccines and for **gene therapy**. The invention provides for the growth and purifn. of adenovirus vectors (helper dependent vectors or HDVs) from which all or most of the viral genes have been removed. The vector system described herein is a new method designed to eliminate helper viruses from the final HDV prepn. by cleavage of the helper virus DNA with an endonuclease, alone or in combination with other methods known to limit the level of helper virus contamination of helper dependent vector prepns. The disclosed methods and compns. also provide for regulated control of gene expression. The invention is exemplified by combining recombinase **Cre**/lox system and restriction endonuclease SceI system. The SceI recognition site is placed between two lox sites flanking the packaging signal, and an internal ITR is inserted to the right of the second lox site. Upon the viral infection of the 293 cells expressing both **Cre** and SceI, SceI can result in a double-stranded break and the adjacent ITR is repaired by panhandle formation (annealing with the right ITR) to form a replicable DNA lacking the packaging signals. For enhanced safety, the site-specific recombinase

Cre can excise the packaging signals in the helper virus genome and prevent them from being packaged with helper dependent adenovirus vector.

L6 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:441823 CAPLUS
DOCUMENT NUMBER: 133:85169
TITLE: Calcium-dependent transcriptional regulator DREAM and its cDNA and methods for drug screening
INVENTOR(S): Naranjo Orovio, Jose Ramon; Mellstrom, Britt; Dompablo Garcia, Isidro; Link, Wolfgang Alexander; Carrion Rodriguez, Angel Manuel; Ledo Gomez, Francisco
PATENT ASSIGNEE(S): Consejo Superior De Investigaciones Cientificas, Spain
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037498	A1	20000629	WO 1999-ES402	19991222

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

ES 2154201	A1	20010316	ES 1998-2667	19981222

PRIORITY APPLN. INFO.: ES 1998-2667 A 19981222
ES 1999-2825 A 19991222

AB Human DREAM and its cDNA as well as use of DREAM for transcriptional silencing of DRE-contg. genes, for regulation of expression of CRE -dependent genes, and for identification of therapeutic substances, is disclosed. Thus, expts. demonstrated the repression of DRE-contg. genes by DREAM and calcium antagonism of this repression. Further expts. indicated that DREAM modulated the activity of CRE-contg. promoters in a calcium-dependent manner via complexes between DREAM and CREB and CREM isoforms. The derepression mediated by cAMP and DRE is specifically mediated by interaction of DREAM and .alpha.CREM. Interaction of DREAM with transcription factors binding to CRE thus appears to be a point of interaction of cAMP- and calcium-mediated intracellular signalling pathways. Mutant forms of DREAM, which bound to CREB and CREM but did not respond to calcium, blocked the activity of these proteins.
REFERENCE COUNT: 5
REFERENCE(S): (1) Carrion, A; MOLECULAR AND CELLULAR BIOLOGY 1998, V18(12), P6921 CAPLUS
(2) Carrion, A; NATURE V398, P80 MEDLINE
(3) Dolmetsch, R; NATURE 1997, V386, P855 CAPLUS
(4) Hardingham, G; NATURE 1997, V385, P260 CAPLUS
(5) Maelicke, A; NACHR CHEM TECH LAN 1999, V47(6), P677 CAPLUS

L6 ANSWER 14 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:161478 CAPLUS
DOCUMENT NUMBER: 132:204060
TITLE: Adenoviruses deleted in the IVa2, 100K and/or preterminal protein sequences
INVENTOR(S): Amalfitano, Andrea; Chen, Yuan Tsong; Hu, Huimin
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 156 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012740	A2	20000309	WO 1999-US19540	19990827
WO 2000012740	A3	20001123		

W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9956942	A1	20000321	AU 1999-56942	19990827

PRIORITY APPLN. INFO.: US 1998-145742 P 19980828
WO 1999-US19540 W 19990827

AB The present invention provides deleted adenovirus vectors. The inventive adenovirus vectors carry one or more deletions in the IVa2, 100K, polymerase and/or preterminal protein sequences of the adenovirus genome.
In the human adenovirus serotype 5 genomes, such deletions are at nucleotide positions 4830-5766, 24,990-25,687, and/or 7274-7991. The adenoviruses may addnl. contain other deletions, mutations or other modifications as well. In particular preferred embodiments, the adenovirus genome is multiply deleted, i.e., carries 2 or more deletions therein. The deleted adenoviruses of the invention are "propagation-defective" in that the virus cannot replicate and produce new virions in the absence of complementing function(s). Preferred adenovirus vectors of the invention carry a heterologous nucleotide sequence encoding a protein or peptide assocd. with a metabolic disorder, more preferably a protein or peptide assocd. with a lysosomal or glycogen storage disease, most preferably, a lysosomal acid .alpha.-glucosidase. The deleted adenovirus vectors advantageously have an increased carrying capacity for heterologous nucleotide sequences, demonstrate lower levels of viral protein expression, induce fewer host immune responses, and/or exhibit increased stability and prolonged transgene expression when introduced into target cells.

L6 ANSWER 15 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:145009 CAPLUS
DOCUMENT NUMBER: 132:204039
TITLE: Methods and compositions for genomic modification by site-specific integration
INVENTOR(S): Calos, Michele P.
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA
SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000011155	A1	20000302	WO 1999-US18987	19990819

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AU 9958985	A1	20000314	AU 1999-58985	19990819

PRIORITY APPLN. INFO.: US 1998-97166 P 19980819
WO 1999-US18987 W 19990819

AB The present invention provides methods of site-specifically integrating a polynucleotide sequence of interest in a genome of a eukaryotic cell, as well as, enzymes, polypeptides, and a variety of vector constructs useful therefore. In the method, a targeting construct comprises, for example, (i) a first recombination site and a polynucleotide sequence of interest, and (ii) a site-specific recombinase, which are introduced into the cell. The genome of the cell comprises a second recombination site. Recombination between the first and second recombination sites is facilitated by the site-specific recombinase. The invention describes compns., vectors, and methods of use thereof, for the generation of transgenic cells, tissues, plants, and animals. The integration

frequency into an attB site located on an EBV plasmid with phage .phi.C31 integrase/recombinase in mammalian cells is impressively high and several orders of magnitude higher than the frequencies of random integration or homologous recombination, highlighting the utilty of this invention. The compns., vectors, and methods of the present invention are also useful in **gene therapy** techniques.
REFERENCE COUNT: 4
REFERENCE(S): (1) McVey; US 5801030 1998 CAPLUS
(2) Reff; US 5830698 A 1998 CAPLUS
(3) Sauer, B; Nucleic Acid Research 1996, V24(23), P4608 CAPLUS
(4) Wahl; US 5654182 A 1997 CAPLUS

L6 ANSWER 16 OF 38 MEDLINE
ACCESSION NUMBER: 2000262155 MEDLINE
DOCUMENT NUMBER: 20262155 PubMed ID: 10800089
TITLE: Functional long-term thymidine kinase suicide gene expression in human T cells using a herpesvirus saimiri vector.
AUTHOR: Hiller C; Wittmann S; Slavin S; Fickenscher H
CORPORATE SOURCE: Institut fur Klinische und Molekulare Virologie, Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany.
SOURCE: GENE THERAPY, (2000 Apr) 7 (8) 664-74.
Journal code: CCE; 9421525. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000606
AB Herpesvirus saimiri transforms human T lymphocytes to stable growth and persists episomally without genomic integration and without virus production. The transformed T cells retain essential features of their parental cells including the MHC-restricted antigen specificity which may be useful for applications in adoptive immunotherapy. In order to improve the biological safety of such vectors, the prodrug activating gene thymidine kinase of herpes simplex virus was inserted into the genome of herpesvirus saimiri by homologous recombination. After infection with wild-type or cloned recombinant viruses, T cells from tamarin monkeys and from humans were transformed to stable growth. Thymidine kinase-expressing transformed T cells were efficiently eliminated in the presence of low concentrations of ganciclovir. This elimination mechanism remained fully functional over an observation period of 12 months. The potentially immunogenic neomycin resistance gene expression cassette was deleted from the genome of established mutant viruses by using the prokaryotic Cre/LoxP recombination system. At any time during the course of a therapeutic application, thymidine kinase-expressing transformed human T cells might be eliminated after administration of ganciclovir. In principle, this function could be useful for the T cell-dependent immunotherapy of resistant blood cancer while avoiding the risk of uncontrolled graft-versus-host disease.

L6 ANSWER 17 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 2000271575 EMBASE
TITLE: Site-specific integration of a **transgene** mediated by a hybrid adenovirus/adeno-associated virus vector using the Cre/loxP-expression-switching system.
AUTHOR: Ueno T.; Matsumura H.; Tanaka K.; Iwasaki T.; Ueno M.; Fujinaga K.; Asada K.; Kato I.
CORPORATE SOURCE: T. Ueno, Biotechnology Research Laboratories, Tahara Shuzo Conpany, Ltd., Shiga 520-2193, Japan
SOURCE: Biochemical and Biophysical Research Communications, (2000) 273/2 (473-478).
Refs: 30
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB As vectors, adenoviruses (Ads) have many attractive advantages for in vivo **gene therapy**. However, Ads do not usually integrate into the host genome and gene expression is, thus, transient. Adeno-associated virus (AAV) integrates into a specific locus (AAVS1) on the human host's chromosome 19, while conventional recombinant AAV (rAAV) vectors do not possess this property because such vectors lack the rep gene. AAV vectors carrying the rep gene do not have enough space for insertion of a **transgene**. We have constructed a hybrid adenovirus/adeno-associated virus (Ad/AAV) vector which has the advantages of both Ads and AAVs. Given that the rep gene products inhibit propagation of Ads, we used the Cre/loxP-expression-switching system to regulate the expression of the rep gene. The Ad/AAV vector easily propagates, can efficiently infect a broad range of cell types, and can integrate into a specific locus on host chromosomes. (C) 2000 Academic Press.

L6 ANSWER 18 OF 38 MEDLINE
ACCESSION NUMBER: 2001025826 MEDLINE
DOCUMENT NUMBER: 20480189 PubMed ID: 11024363
TITLE: Site-specific gene targeting for gene expression in eukaryotes.
AUTHOR: Gorman C; Bullock C
CORPORATE SOURCE: DNA Bridges, Inc., San Francisco, CA 94117, USA..
cori@dnabridges.com
SOURCE: CURRENT OPINION IN BIOTECHNOLOGY, (2000 Oct) 11 (5) 455-60.
Ref: 39
Journal code: A92. ISSN: 0958-1669.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001113
AB Major advances in the use of site-specific recombinases to facilitate sustained gene expression via chromosomal targeting have been made during the past year. New tools for genomic manipulations using this technology include the discovery of epitopes in recombinases that confer nuclear localization, crystal structures that show the precise topology of recombinase-DNA-substrate synaptic complexes, manipulations of the DNA recognition sequences that select for integration over excision of DNA, and manipulations that make changes in gene expression inducible by drug administration. In addition, endogenous eukaryotic and mammalian DNA sequences have been discovered that can support site-specific recombinase-mediated manipulations.

L6 ANSWER 19 OF 38 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 2000:54417 LIFESCI
TITLE: Targeted expression of baculovirus p35 caspase inhibitor in oligodendrocytes protects mice against autoimmune-mediated demyelination
AUTHOR: Hisahara, S.; Araki, T.; Sugiyama, F.; Yagami, K.; Suzuki, M.; Abe, K.; Yamamura, K.; Miyazaki, J.; Momoi, T.; Saruta, T.; Bernard, C.C.A.; Okano, H.; Miura, M.
CORPORATE SOURCE: Division of Neuroanatomy, Department of Neuroscience, Biomedical Research Center (D-12), Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; E-mail: mmiura@nana.med.osaka-u.ac.jp
SOURCE: EMBO Journal [EMBO J.], (20000201) vol. 19, no. 3, pp. 341-348.
ISSN: 0261-4189.
DOCUMENT TYPE: Journal
FILE SEGMENT: G; V; F
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The mechanisms underlying oligodendrocyte (OLG) loss and the precise roles played by OLG death in human demyelinating diseases such as multiple

sclerosis (MS), and in the rodent model of MS, experimental autoimmune encephalomyelitis (EAE), remain to be elucidated. To clarify the involvement of OLG death in EAE, we have generated **transgenic** mice that express the baculovirus anti-apoptotic protein p35 in OLGs through the Cre-loxP system. OLGs from cre/p35 **transgenic** mice were resistant to tumor necrosis factor- alpha -, anti-Fas antibody- and interferon- gamma -induced cell death. cre /p35 **transgenic** mice were resistant to EAE induction by immunization with the myelin oligodendrocyte glycoprotein. The numbers of infiltrating T cells and macrophages/microglia in the EAE lesions were significantly reduced, as were the numbers of apoptotic OLGs expressing the activated form of caspase-3. Thus, inhibition of apoptosis in OLGs by p35 expression alleviated the severity of the neurological manifestations observed in autoimmune demyelinating diseases.

L6 ANSWER 20 OF 38 MEDLINE
ACCESSION NUMBER: 2000435689 MEDLINE
DOCUMENT NUMBER: 20393196 PubMed ID: 10933949
TITLE: Stable transduction of actively dividing cells via a novel adenoviral/episomal vector.
AUTHOR: Leblois H; Roche C; Di Fabo N; Orsini C; Yeh P; Perricaudet M
CORPORATE SOURCE: Institut Gustave Roussy, CNRS-IGR-Rhone Poulenc Rorer UMR 1582, Villejuif, France.. lebbis@igr.fr
SOURCE: MOLECULAR THERAPY, (2000 Apr) 1 (4) 314-22. Journal code: DRT; 100890581. ISSN: 1525-0016.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000918

AB Many **gene therapy** indications would benefit from vectors capable of achieving efficient in vivo delivery and long-term **transgene** expression in either dividing or nondividing cells. Such vector systems are not yet available. To achieve both goals, we have used noncytotoxic E1- and E4-deleted adenoviral vectors as vehicles for delivering an Epstein-Barr virus-based self-replicating episome (replicon) via Cre/loxP site-specific recombination. Co-infection of human cells with a proreplicon-encoded and a Cre-expressing adenovirus resulted in efficient delivery and excision of a functional replicon in the absence of vector-induced cytotoxicity. In addition, replication and nuclear retention of the replicon in the cell progeny translated into a prolonged **transgene** expression in actively dividing cells, both in vitro and in vivo. Combining desired features from different viruses within a single hybrid vector system should expand the range of clinical indications currently amenable to gene transfer.

L6 ANSWER 21 OF 38 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 2001:27148 LIFESCI
TITLE: Inducible and irreversible control of gene expression using a single **transgene**
AUTHOR: Fuhrmann-Benzakein, E.; Garcia-Gabay, I.; Pepper, M.S.; Vassalli, J.-D.; Herrera, P.L.
CORPORATE SOURCE: Department of Morphology and, University of Geneva Medical School, 1 Rue Michel-Servet, CH-1211 Geneva 4, Switzerland; E-mail: pedro.herrera@medecine.unige.ch
SOURCE: Nucleic Acids Research [Nucleic Acids Res.], (20001201) vol. 28, no. 23, e99. ISSN: 0305-1048.
DOCUMENT TYPE: Journal
FILE SEGMENT: N
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Experimental or therapeutic designs involving the conditional expression of genes often require the use of two different **transgenes**; this can represent a major undertaking. One of these systems takes advantage of inducible recombinases. Here we show a novel use of such enzymes, in that an inducible recombinase-encoding sequence can function to both block the transcription of a gene placed downstream and, subsequently, irreversibly activate transcription of this very same gene. This double function, which circumvents the need for two **transgenes**, can be achieved by flanking the inducible recombinase gene by two of its target sequences. In our design we used as the inducible recombinase gene the Cre-ER super(T) gene flanked by two loxP sites. This cassette was placed between a mouse phosphoglycerate kinase promoter and the enhanced green fluorescent protein (EGFP) coding sequence. Massive EGFP gene expression in BHK cells bearing this **transgene** was observed upon administration of 4-hydroxytamoxifen (4-OHT), the inducer of the recombinant activity of Cre-ER super(T). In the absence of 4-OHT EGFP production was prevented. Because of its simplicity (only a single **transgene** needs to be used) this strategy is of obvious interest in certain protocols of gene or cell therapy and in a variety of experimental designs in which conditional expression of genes is required.

L6 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:736961 CAPLUS
DOCUMENT NUMBER: 131:347505
TITLE: Novel helper free lentiviral packaging cell lines for usage in **gene therapy**
INVENTOR(S): Leboulch, Philippe; Westerman, Karen
PATENT ASSIGNEE(S): Genetix Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 39 pp. CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958701	A1	19991118	WO 1999-US10585	19990513

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9939887	A1	19991129	AU 1999-39887	19990513
EP 1076715	A1	20010221	EP 1999-923020	19990513

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: US 1998-85283 P 19980513
WO 1999-US10585 W 19990513

AB Novel packaging cell lines which produce recombinant retrovirus, free of detectable helper-virus are disclosed. Also disclosed are methods of making the cell lines and methods of producing recombinant retroviruses from the cell lines. Retroviruses produced by the cell lines include lentiviruses, such as HIV, capable of transfering heterologous DNA to a wide range of non-dividing cells. The packaging cells contain at least three vectors which collectively encode retroviral gag, pol, and env proteins, wherein the gag and pol genes are sepd., in part, onto two or more different vectors. This is made possible by fusing Vpr or Vpx to pol proteins sepd. from gag so that the proteins are targeted to assembling virions. Among other advantages, the packaging cells provide the benefit of increased safety when used in human **gene therapy** by virtually eliminating the possibility of mol. recombination leading to prodn. of replication-competent helper virus.

REFERENCE COUNT: 3
REFERENCE(S): (1) Gallay, P; WO 9812314 A 1998 CAPLUS
(2) Kingsman, A; WO 9817815 A 1998 CAPLUS
(3) Richardson, J; Journal of General Virology 1995, V76(3), P691 CAPLUS

L6 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:350740 CAPLUS
DOCUMENT NUMBER: 131:14860
TITLE: Nucleic acids involved in the murine T/t-complex Responder phenotype and their diagnostic and

therapeutic applications
INVENTOR(S): Herrmann, Bernhard; Koschorz, Birgit; Kispert, Andreas
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Forderung der Wissenschaften E.V., Germany
SOURCE: PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925815	A2	19990527	WO 1998-EP7395	19981118
WO 9925815	A3	19990819		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9916711	A1	19990607	AU 1999-16711	19981118
EP 1032595	A2	20000906	EP 1998-961219	19981118

R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE
PRIORITY APPLN. INFO.: EP 1997-120190 A 19971118
EP 1998-103596 A 19980302
WO 1998-EP7395 W 19981118

AB The present invention relates to nucleic acid mols. encoding expression products involved in the Responder function, which contributes to the phenomenon of transmission ratio distortion. The present invention also relates to regulatory regions of the genes corresponding to said nucleic acid mols. The mouse Tlt-complex, a region of .apprx.12 cM genetic distance on the proximal part of chromosome 17, contains several loci acting in concert to produce a phenomenon called transmission ration distortion, indicating the fact that the so-called t-haplotype form of this chromosomal region has a selective advantage over the wild type form in that it is transmitted to the offspring at non-Mendelian ratios of up to 99%. The cDNA sequences of T66Bk mols. contain MARK2 kinase and rsk3 kinase homol. regions; T66Bk-2 cDNA contains only the MARK kinase homol. region, T66k-8 cDNA contains the complete sequence of T66Bk-2 except for a single base deleted resulting in a frameshift, T66k-7 cDNA corresponds to an antisense transcript of a T66Bk family member, and T66k-20 shows a strong similarity to the above members of the T66Bk gene family. Addnl. variants of the T66k family are shown from various mouse strains. The Responder function is located in the T66B region, is expressed in testis, and is expressed during spermatogenesis. Thus, the t-Responder may act as a component of a signaling cascade involved in sperm motility and/or the fertilization of oocytes and relates to methods of influencing transmission ratio. The present invention further relates to recombinant DNA mols. and vectors comprising said nucleic acid mols. and/or regulatory regions as well as to host cells transformed therewith. Addnl., the present invention relates to **transgenic** animals, comprising said nucleic acid mols., recombinant DNA mols. or vectors stably integrated into their genome. The various embodiments of the invention have a significant impact on breeding strategies by allowing for the specific selection of genetic traits and in particular of sex. Further, the present invention finds applications in the development of contraceptives.

L6 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:286096 CAPLUS
DOCUMENT NUMBER: 130:321603
TITLE: Transcriptionally-activated inverted terminal repeats of adeno-associated virus (AAV) for use in recombinant AAV vectors
INVENTOR(S): Feldhaus, Andrew L.
PATENT ASSIGNEE(S): Targeted Genetics Corporation, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9920773	A2	19990429	WO 1998-US21937	19981020
WO 9920773	A3	19990701		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9910966	A1	19990510	AU 1999-10966	19981020
EP 1025243	A2	20000809	EP 1998-953639	19981020

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: US 1997-955400 A 19971021
WO 1998-US21937 W 19981020
AB This invention provides transcriptionally-activated inverted terminal repeats (ITRs) of AAV. The ITRs are less < 400 bp and comprises heterologous transcriptionally active elements which exhibit at least about a two-fold increase in their activities relative to that of a wild-type ITR. These features provide the expression of relatively large **transgenes** packaged in recombinant AAV vectors for **gene therapy**. The AAV-derived vector was used to express the human cystic fibrosis transmembrane regulator (CFTR) cDNA.

L6 ANSWER 25 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
ACCESSION NUMBER: 1999344925 EMBASE
TITLE: Use of helper-dependent adenoviral vectors of alternative serotypes permits repeat vector administration.
AUTHOR: Parks R.J.; Evelegh C.M.; Graham F.L.
CORPORATE SOURCE: F.L. Graham, Department of Biology, McMaster University, 1280 Main Street West, Hamilton, Ont. L8S 4K1, Canada
SOURCE: Gene Therapy, (1999) 6/9 (1565-1573).
Refs: 74
ISSN: 0969-7128 CODEN: GETHEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have developed a new helper adenovirus (Ad) based on serotype 2, Ad2LC8cCARP, for use in the Cre/loxP system to generate Ad vectors deleted of all protein coding sequences (helper-dependent Ad vectors (hdAd)). A comparison of Ad2LC8cCARP and our original helper virus (based on serotype 5, Ad5LC8cluc) showed that the two helper viruses amplified hdAd with a similar efficiency, and resulted in a similar yield and purity after large-scale preparation of vector. In vitro, the resulting hdAd2 had a similar transduction efficiency and expression kinetics of **transgene** (.beta.-gal) as the hdAd5. An important feature of the helper-dependent system is that all virion components, except the virion DNA, derive from the helper virus. Consequently, vectors produced with help from Ad2LC8cCARP were not neutralized by antibodies against Ad5, and vectors produced with Ad5 helper were resistant to neutralizing antibodies against Ad2. Analysis of **transgene** expression in mouse liver after intravenous injection of the Ad2-based hdAd showed that the vector could efficiently transduce the liver and produce high levels of a foreign **transgene**, similar to those expressed by the hdAd generated with the Ad5 helper virus. Mice immunized with hdAd2 produced Ad2-neutralizing antibodies, which did not cross-react with hdAd5. To determine if successful repeat Ad vector administration could be achieved by sequential use of alternative Ad serotypes, we injected mice with hdAd2 (hSEAP) followed 3 months later by a lacZ-expressing hdAd of either the same or different serotype. Repeated administration of hdAd2 resulted in a 30- to 100-fold reduction in

transgene expression compared with naive animals. In contrast, no decrease in transgene expression was observed when the second vector was of a different serotype. These results demonstrate that effective vector readministration can be achieved by the sequential use of hdAds based on alternative serotypes.

L6 ANSWER 26 OF 38 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 1999:72103 LIFESCI
TITLE: Impaired myocardial angiogenesis and ischemic cardiomyopathy in mice lacking the vascular endothelial growth factor isoforms VEGF sub(164) and VEGF sub(188)
AUTHOR: Carmeliet, P.; Ng, Y.-S.; Nuyens, D.; Theilmeier, G.; Brusselmans, K.; Cornelissen, I.; Ehler, E.; Kakkar, V.V.; Stalmans, I.; Mattot, V.; Perriard, J.-C.; Dewerchin, M.; Flameng, W.; Nagy, A.; et al.,
CORPORATE SOURCE: The Center for Transgene Technology and Gene Therapy, Flanders Interuniversity Institute for Biotechnology, KU Leuven, Leuven, B-3000, Belgium; E-mail: peter.carmeliet@med.kuleuven.ac.be
SOURCE: Nature Medicine [Nat. Med.], (19990500) vol. 5, no. 5, pp. 495-502. ISSN: 1078-8956.
DOCUMENT TYPE: Journal
FILE SEGMENT: W3; G
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The gene for vascular endothelial growth factor (VEGF) encodes three spliced isoforms. Although the heparin binding capacities of these isoforms differ, little is known about their differential functions in vivo. We generated mice expressing exclusively the VEGF sub(120) isoform (VEGF super(120/120) mice) by Cre/loxP-mediated removal of exons 6 and 7, which encode the isoforms of 164 and 188 amino acids. VEGF super(120/120) mice had impaired postnatal myocardial angiogenesis, resulting in ischemic cardiomyopathy characterized by reduced contractility and sarcomere breakdown, but normal stores of high-energy phosphates. VEGF super(120/120) mice ultimately died of cardiac failure. The VEGF super(120/120) mouse model may be useful for studying the molecular mechanisms of the myocardial response to ischemia and for testing the angiogenic properties of different VEGF isoforms. Vascular endothelial growth factor (VEGF) is involved in embryonic and pathological vascular development. It may also be involved in the angiogenic response to myocardial ischemia and is now being tested for use in gene therapy of ischemic heart and tissue disease. The mouse VEGF gene is alternatively transcribed to produce at least three isoforms: VEGF sub(120), VEGF sub(164) and VEGF sub(188). VEGF sub(120) is diffusible in the extracellular milieu, whereas the longer isoforms show increasing binding to heparan sulfate-rich matrix. These isoforms differ in their mitogenicity, chemotactic properties, receptor binding characteristics and tissue-specific expression. However, it remains controversial whether the isoforms differ in specificity, potency or quality for their role in normal, pathological or therapeutical angiogenesis in vito. Nevertheless, gene therapy protocols now use VEGF sub(120) or VEGF sub(164) indiscriminately for improvement of tissue ischemia. As the loss of a single VEGF allele results in embryonic lethality due to severe vascular defects, it is not possible to study the role of VEGF during postnatal angiogenic processes by conventional transgene technology. Therefore, we generated mice expressing only VEGF sub(120) (VEGF super(120/120) mice) using the Cre/loxP system to remove exons 6 and 7, which encode basic domains that are only present in VEGF sub(164) and/or VEGF sub(188). The absence of VEGF sub(164) and VEGF sub(188) impaired myocardial angiogenesis, leading to ischemic cardiomyopathy.

L6 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:176034 CAPLUS
DOCUMENT NUMBER: 128:214185
TITLE: Use of the cre-loxP system to control expression of genes in the manufacture of adenovirus vectors for gene therapy
INVENTOR(S): Wilson, James M.; Phaneuf, Daniel
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA;
Wilson, James M.; Phaneuf, Daniel
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9810086	A1	19980312	WO 1997-US15691	19970904
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9741830	A1	19980326	AU 1997-41830	19970904
AU 722375	B2	20000803		
EP 950111	A1	19991020	EP 1997-939821	19970904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001500014	T2	20010109	JP 1998-512948	19970904

PRIORITY APPLN. INFO.: US 1996-25323 P 19960906
WO 1997-US15691 W 19970904
AB A method for the manuf. of adeno-assocd. virus carrying a foreign gene in which the cre-loxP system is used to regulate expression of the rep/cap genes is described. Regulated expression of these genes allows efficient packaging of a gene flanked by adeno-assocd. virus inverted terminal repeats without a build up of toxic levels of the rep gene product. The method uses three vectors. A first vector is an expression vector for the cre gene, the second is an expression vector for the rep/cap genes in which the promoter is sepd. from the coding region by an insert flanked by loxP sites and rep/cap, and a third vector contains a minigene contg. a transgene and regulatory sequences flanked by AAV ITRs. The third vector contains an expression cassette for the therapeutic gene flanked by AAV inverted terminal repeats. The host cell stably or inducibly expresses the cre gene and two vectors carrying the other elements of the system are introduced into the host cell.

L6 ANSWER 28 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5
ACCESSION NUMBER: 1998236963 EMBASE
TITLE: An adenoviral vector deleted for all viral coding sequences results in enhanced safety and extended expression of a leptin transgene.
AUTHOR: Morsy M.A.; Gu M.; Motzel S.; Zhao J.; Lin J.; Su Q.; Allen H.; Franlin L.; Parks R.J.; Graham F.L.; Kochanek S.; Bett A.J.; Caskey C.T.
CORPORATE SOURCE: M.A. Morsy, Department of Human Genetics, Merck Research Laboratories, West Point, PA 19486, United States. morsy@merck.com
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (7 Jul 1998) 95/14 (7866-7871). Refs: 36 ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Adenoviral (Ad)-mediated in vivo gene transfer and expression are limited in part by cellular immune responses to viral-encoded proteins and/or transgene immunogenicity. In an attempt to diminish the former responses, we have previously developed and described helper-dependent (HD) Ad vectors in which the viral protein coding sequences are completely eliminated. These HD vectors have up to 37 kb insert capacity, are easily

propagated in a Cre recombinase-based system, and can be produced to high concentration and purity (>99.9% helper-free vector). In this study, we compared safety and efficacy of leptin gene delivery mediated by an HD vector (HD-leptin) and a first-generation E1-deleted Ad vector (Ad-leptin) in normal lean and ob/ob (leptin-deficient) mice. In contrast to evidence of liver toxicity, inflammation, and cellular infiltration observed with Ad-leptin delivery in mice, HD-leptin delivery was associated with a significant improvement in associated safety/toxicity and resulted in efficient gene delivery, prolonged elevation of serum leptin levels, and associated weight loss. The greater safety, efficient gene delivery, and increased insert capacity of HD vectors are significant improvements over current Ad vectors and represent favorable features especially for clinical gene therapy applications.

L6 ANSWER 29 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
DUPLICATE 6
ACCESSION NUMBER: 1998:404618 BIOSIS
DOCUMENT NUMBER: PREV199800404618
TITLE: Efficient Fas-ligand gene expression in rodent liver after intravenous injection of a recombinant adenovirus by the use of a Cre-mediated switching system.
AUTHOR(S): Okuyama, T. (1); Fujino, M.; Li, X.-K.; Funeshima, N.; Kosuga, M.; Saito, I.; Suzuki, S.; Yamada, M.
CORPORATE SOURCE: (1) Dep. Genet., Natl. Child. Med. Res. Cent., 3-35-31 Taishido, Setagaya-ku, Tokyo 154-8509 Japan
SOURCE: Gene Therapy, (Aug., 1998) Vol. 5, No. 8, pp. 1047-1053. ISSN: 0969-7128.
DOCUMENT TYPE: Article
LANGUAGE: English
AB An adenovirus vector AxCALNFasL was constructed in order to transduce a gene for rat Fas-ligand, requiring co-expression of Cre recombinase for its expression. In the cosmid cassette, pAxCALNFasL, a stuffer DNA fragment flanked with two loxP sequences was placed between the promoter and Fas-ligand cDNA to prevent its expression in transfected 293 cells. COS-7 cells infected with AxCALNFasL alone did not induce apoptosis in cocultivated Jurkat cells, but the cells treated with AxCALNFasL and AxCANCre (an adenovirus expressing Cre recombinase with the CAG promoter) did. BALB/c mice injected with 109 plaque-forming units of AxCALNFasL and with different doses of AxCANCre, developed lethal acute liver failure. The number of the apoptotic hepatocytes increased dramatically with increased doses of injected AxCANCre, indicating that the level of transgene expression in the rodent liver appeared to be adjustable. Based on these observations, we conclude that vectors expressing a gene to produce cytotoxic substances can be constructed by the use of a Cre-mediated switching system. Our system also demonstrated that efficient expression of the toxic gene in the rodent liver was achievable by co-infection of adenovirus vectors carrying the target gene and Cre recombinase.

L6 ANSWER 30 OF 38 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 1998:79662 LIFESCI
TITLE: Generation of a conditionally neo super(r)-containing retroviral producer cell line: effects of neo super(r) on retroviral titer and transgene expression
AUTHOR: Wildner, O.; Candotti, F.; Krecko, E.G.; Xanthopoulos, K.G.; Ramsey, W.J.; Blaese, R.M.
CORPORATE SOURCE: Clinical Gene Therapy Branch, NHGRI, NIH, Building 10, Room 10C103, 10 Center Drive, MSC 1851, Bethesda, MD, 20892-1851, USA
SOURCE: Gene Ther., (19980500) vol. 5, no. 5, pp. 684-691. ISSN: 0969-7128.
DOCUMENT TYPE: Journal
FILE SEGMENT: W3
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have developed a method for generating high-titer retroviral producer cell lines conditionally containing a neomycin resistance gene (neo super(r)) based on the Cre/loxP system. For this, a bicistronic retroviral splicing vector carrying the green fluorescence protein (GFP) and a marker gene cassette consisting of internal ribosome entry site (IRES) and neo super(r) flanked by loxP sites, was constructed and conveniently used to generate a G418 resistant vector producer cell line. Following titer determination and verification of the biological activity of the retroviral supernatants, the selectable expression cassette which was no longer required was excised from the provirus by transient Cre expression using an adenoviral vector. This strategy led to precise excision of neo super(r) and generation of retroviral supernatants containing functional 'neo-less' retroviral particles without detrimental effects on the high vector titers found in the parental neo super(r)-containing producer lines. GFP expression was significantly increased after the excision of neo super(r), in both the producer lines and retrovirally transduced target cells. Reintroduction of neo super(r) did not alter GFP expression, suggesting that the neo super(r) gene and/or its gene product per se are not acting as a transcriptional silencer.

L6 ANSWER 31 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:15860 CAPLUS
DOCUMENT NUMBER: 128:85158
TITLE: Use of retrovirus vectors and the cre/lox system to achieve efficient, stable, site-specific integration of transforming DNA
INVENTOR(S): Leboulch, Philippe; Bouhassira, Eric; Westerman, Karen; Takekoshi, Ken Julian
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA; Albert Einstein College of Medecine of Yeshiva University
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9747758	A1	19971218	WO 1997-US9954	19970606
US 5928914	A	19990727	US 1996-743796	19961105
CA 2258007	AA	19971218	CA 1997-2258007	19970606
AU 9733062	A1	19980107	AU 1997-33062	19970606
AU 733016	B2	20010503		
EP 914457	A1	19990512	EP 1997-928910	19970606
JP 2000512150	T2	20000919	JP 1998-501738	19970606

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1996-664084 A 19960614
US 1996-743796 A 19961105
WO 1997-US9954 W 19970606
AB A transformation method that results in efficient and stable site-specific integration of transforming DNA is described. Transformation is achieved by introducing into a cell an acceptor vector, preferably a retroviral vector, that integrates into the genome of the cell. The acceptor vector comprises two incompatible lox sequences, L1 and L2, that differ by a few bases and that cannot recombine with one another. A donor vector carrying a transgene flanked by the same L1 and L2 sequences is then introduced into the transformed cells. Stable gene transfer is initiated by cre recombinase-mediated recombination of the lox L1 and L2 sequences. A retrovirus is used for the first transformation because of its site-specific integration. Any suitable vector, such as an adeno-assocd. virus, may be used for the second transformation.

L6 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:579821 CAPLUS
DOCUMENT NUMBER: 127:243992
TITLE: Glucocorticoid receptor with modified ligand specificity, fusion proteins containing the ligand binding domain thereof, and their use in controlling gene expression in recombinant cells and transgenic animals

INVENTOR(S): Brocard, Jacques Bertrand; Chambon, Pierre Henri; Gronemeyer, Hinrich; Metzger, Daniel; Nicolas, Jean-Claude; Roux, Sylvie
PATENT ASSIGNEE(S): Association pour le Developpement de la Recherche, Fr.; Brocard, Jacques Bertrand; Chambon, Pierre Henri; Gronemeyer, Hinrich; Metzger, Daniel; Nicolas, Jean-Claude; Roux, Sylvie
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9731108	A1	19970828	WO 1997-FR315	19970220
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
FR 2745008	A1	19970822	FR 1996-2060	19960220
CA 2247517	AA	19970828	CA 1997-2247517	19970220
AU 9720989	A1	19970910	AU 1997-20989	19970220
AU 707684	B2	19990715		
EP 896620	A1	19990217	EP 1997-906232	19970220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000505298	T2	20000509	JP 1997-529854	19970220

PRIORITY APPLN. INFO.: FR 1996-2060 19960220
WO 1997-FR315 19970220

AB A DNA fragment coding for a modified nuclear glucocorticoid receptor, particularly one mutated in the region coding for the ligand binding domain, so that receptor activity is more strongly inducible by a synthetic glucocorticoid ligand than by a natural glucocorticoid ligand, is disclosed. A fusion protein between the modified ligand-binding domain of the glucocorticoid receptor and a DNA-binding domain may be used to control gene expression in recombinant cells or in transgenic animals. A recombination system inducible in mammals by means of a fusion protein produced between a recombinase and the binding domain of the ligand derived from the modified glucocorticoid receptor of which the activity is more strongly inducible by synthetic glucocorticoids than by natural glucocorticoids, is also disclosed. The human glucocorticoid receptor contg. threonine at position 747 instead of isoleucine displays normal transactivating activity with dexamethasone, but not with natural ligands aldosterone and corticosterone. COS-7 cells contg. a reporter gene controlled by a GRE were exposed to dexamethasone or corticosterone. Reporter gene expression was only obsd. with the synthetic glucocorticoid. Control of genetic recombination (i.e., excision of loxP-flanked gene insert) in cells or transgenic mice by modified glucocorticoid receptor ligand binding domain fused to Cre recombinase was also demonstrated.

L6 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:601803 CAPLUS
DOCUMENT NUMBER: 125:240227
TITLE: Materials and methods for regulating polypeptide production in animal cells and their clinical application
INVENTOR(S): Thorens, Bernard
PATENT ASSIGNEE(S): Ecole Polytechnique Federale De Lausanne, Switz.; Universite De Lausanne; Centre Hospitalier Universitaire Vaudois; Kiddle, Simon John
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9625487	A1	19960822	WO 1996-GB256	19960207
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE				
CA 2211101	AA	19960822	CA 1996-2211101	19960207
AU 9646295	A1	19960904	AU 1996-46295	19960207
AU 699061	B2	19981119		
EP 809692	A1	19971203	EP 1996-901901	19960207
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 11505102	T2	19990518	JP 1996-524735	19960207
US 6074875	A	20000613	US 1998-912946	19980304

PRIORITY APPLN. INFO.: GB 1995-2830 A 19950214
WO 1996-GB256 W 19960207

AB This application relates to cell lines transfected with (a) nucleic acid encoding one or more hormone receptors, the receptors being capable of transmitting a signal; and (b) nucleic acid encoding a desired polypeptide, the nucleic acid encoding the polypeptide being under the control of a promoter contg. regulatory elements (e.g. CRE) responsive to the signal transmitted by the receptor(s) so that transcription of the nucleic acid encoding the desired polypeptide is modulated by the level of the hormone(s) in the patient. Preferably, the receptors are the GIP (gastric inhibitory polypeptide) or GLP-1 (glucagon-related peptide I) receptors controlling the prodn. of insulin in the cells in response to changes in the metabolic status of a patient. The methods are useful in controlling metabolic diseases such as type I or type II diabetes or obesity.

L6 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:350220 CAPLUS
DOCUMENT NUMBER: 125:27701
TITLE: Regulatable elimination of gene expression, gene product function and engineered host cells, and its application in gene therapy
INVENTOR(S): Brugge, Joan S.; Crabtree, Gerald R.
PATENT ASSIGNEE(S): Ariad Gene Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 141 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9606111	A1	19960229	WO 1995-US10591	19950818
W: AU, CA, GB, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5834266	A	19981110	US 1994-292597	19940818
AU 9534092	A1	19960314	AU 1995-34092	19950818
EP 776335	A1	19970604	EP 1995-930868	19950818
R: AT, CH, DE, FR, GB, LI, SE				
JP 10507624	T2	19980728	JP 1995-508238	19950818

PRIORITY APPLN. INFO.: US 1994-292595 A 19940818
US 1994-292596 A 19940818
US 1994-292597 A 19940818
US 1993-17931 B2 19930212
US 1993-92977 B2 19930716
US 1993-93499 A2 19930716
US 1994-179143 B2 19940107
US 1994-179748 A2 19940107
WO 1995-US10591 W 19950818

AB Materials and methods are disclosed for regulated obstruction of the expression of a target gene or the biol. effect of its gene product in genetically engineered cells or organisms contg. them. Aspects of the invention are exemplified by recombinant modifications of host cells and their use in vitro and in vivo for the regulatable blockade of expression of a target gene, for interference with the function or effect of a target gene product or for the regulatable elimination of a target gene. Synthesis of oligomer of ligands such as FK506 and cyclosporin A, and regulation of programmed cell death with immunophilin-Fas antigen chimeras were demonstrated.

L6 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:524191 CAPLUS
DOCUMENT NUMBER: 125:213589
TITLE: Reversible immortalization of mammalian cells mediated by retroviral transfer and site-specific recombination
AUTHOR(S): Westerman, Karen A.; Leboulch, Philippe
CORPORATE SOURCE: Div. Health Sciences Technology, Massachusetts Inst. Technology, Cambridge, MA, 02139, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1996), 93(17), 8971-8976

CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A procedure of reversible immortalization of primary cells was devised by retrovirus-mediated transfer of an oncogene that could be subsequently excised by site-specific recombination. This study focused on the early stages of immortalization: global induction of proliferation and life span extension of cell populations. Comparative anal. of Cre/LoxP and FLP/FRT recombination in this system indicated that only Cre /LoxP operates efficiently in primary cells. Cells reverted to their preimmortalized state, as indicated by changes in growth characteristics and p53 levels, and their fate conformed to the telomere hypothesis of replicative cell senescence. By permitting temporary and controlled expansion of primary cell populations without retaining the transferred oncogene, this strategy may facilitate **gene therapy** manipulations of cells unresponsive to exogenous growth factors and make practical gene targeting by homologous recombination in somatic cells. The combination of retroviral transfer and site-specific recombination should also extend gene expression studies to situations previously inaccessible to experimentation.

L6 ANSWER 36 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 7
ACCESSION NUMBER: 96344509 EMBASE
DOCUMENT NUMBER: 1996344509
TITLE: Recombinant adenoviruses with large deletions generated by Cre-mediated excision exhibit different biological properties compared with first- generation vectors in vitro and in vivo.
AUTHOR: Lieber A.; He C.-Y.; Kirillova I.; Kay M.A.
CORPORATE SOURCE: Division of Medical Genetics, Department of Medicine, University of Washington,Seattle, WA 98195, United States
SOURCE: Journal of Virology, (1996) 70/12 (8944-8960). ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In vivo gene transfer of recombinant E1-deficient adenoviruses results in early and late viral gene expression that elicits a host immune response, limiting the duration of **transgene** expression and the use of adenoviruses for **gene therapy**. The prokaryotic Cre-lox P recombination system was adapted to generate recombinant adenoviruses with extended deletions in the viral genome (referred to here as deleted viruses) in order to minimize expression of immunogenic and/or cytotoxic viral proteins. As an example, an adenovirus with a 25.kb deletion that lacked E1, E2, E3, and late gene expression with viral titers similar to those achieved with first-generation vectors and less than 0.5% contamination with E1-deficient virus was produced. Gene transfer was similar in HeLa cells, mouse hepatoma cells, and primary mouse hepatocytes in vitro and in vivo as determined by measuring reporter gene expression and DNA transfer. However, **transgene** expression and deleted viral DNA concentrations were not stable and declined to undetectable levels much more rapidly than those found fur first-generation vectors. Intravenous administration of deleted vectors in mice resulted in no hepatocellular injury relative to that seen with first-generation vectors. The mechanism for stability of first-generation adenovirus vectors (E1a deleted) appeared to be linked in part to their ability to replicate in transduced cells in vivo and in vitro. Furthermore, the deleted vectors were stabilized in the presence of undeleted first-generation adenovirus vectors. These results have important consequences for the development of these and other nonintegrating vectors fur **gene therapy**.

L6 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:654426 CAPLUS
DOCUMENT NUMBER: 125:294260
TITLE: Regulatable promoters for use in **gene therapy** applications: Modification of the 5'-flanking region of the CFTR gene with multiple cAMP response elements to support basal, low-level gene expression that can be upregulated by exogenous agents that raise intracellular levels of cAMP
AUTHOR(S): Suzuki, Motoyoshi; Singh, Ravi N.; Crystal, Ronald G.
CORPORATE SOURCE: Cornell Medical Center, New York Hospital, New York, NY, 10021, USA
SOURCE: Hum. Gene Ther. (1996), 7(15), 1883-1893 CODEN: HGTHE3; ISSN: 1043-0342
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study focuses on the design, construction, and evaluation of a chimeric promoter for **gene therapy** applications where it is desirable to have low-level basal expression of the newly transferred gene, which can be induced to higher levels of expression by the administration of pharmacol. agents that can be safely used locally and/or systemically in humans. To achieve this, a chimeric promoter was constructed using fragments of the 5'-flanking region of the human cystic fibrosis transmembrane conductance regulator (CFTR) gene, and multiple tandem repeats of the consensus sequence and flanking elements of the cAMP response element (**CRE**), promoter sequences that support increased transcription in response to elevations in intracellular cAMP levels. Preliminary studies using plasmid vectors demonstrated that: (i) the 5'-flanking sequences from the CFTR gene have low promoter activity in the human airway epithelial cell lines; (ii) chimeras using -718 bp fragment from the 5'-flanking sequence of CFTR gene as the base, with the addn. of 4-10 units of a 25-bp sequence contg. the **CRE** consensus sequence, were all inducible by a rise in intracellular cAMP, with the chimera having eight **CRE** repeats the most responsive; and (iii) a CF126(CRE8) chimera, consisting of the -126 bp fragment from the 5'-flanking region of CFTR gene together with eight **CRE** repeats, yielded low-level basal activity but maximal upregulation by cAMP, resulting in expression of the reporter gene that was 51-58% of an RSV-LTR control. On the basis of these observations, replication-deficient adenoviral vectors contg. the CF126(CRE8) chimera and the luciferase reporter gene [AdCF126(CRE8).Luc] or the Escherichia coli lacZ (.beta.-Gal) reporter gene [AdCF126(CRE8)..beta.gal] were constructed. In several human airway epithelial cell lines, the AdCF126 (**CRE**).Luc vector provided low basal activity, but was significantly upregulated by agents that increase cAMP levels. Intranasal administration of the .beta.-Gal-expressing AdCF126(CRE8).beta.gal vector into C57B1/6 mice demonstrated cAMP-induced upregulation of the reporter gene in airway epithelial cells. Quantification of the inducibility of the chimeric promoter activity in the airway epithelium using the AdCF126(CRE8).Luc vector demonstrated an 11-fold upregulation of the basal promoter activity in the lung with the administration of a phosphodiesterase inhibitor and a cAMP analog. These observations demonstrate the feasibility of using a chimeric promoter comprised of a minimal fragment of the CFTR 5'-flanking region, together with added multiple **CRE**, to control genes delivered in vivo. Importantly, because there are many drugs used in humans that raise cAMP, the concept of using a cAMP-regulatable promoter may also be a useful approach to enhance the safety, efficacy, and feasibility of a variety of human **gene therapy** strategies.

L6 ANSWER 38 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 8
ACCESSION NUMBER: 92102575 EMBASE
DOCUMENT NUMBER: 1992102575
TITLE: Identification of cryptic lox sites in the yeast genome by selection for Cre-mediated chromosome translocations that confer multiple drug resistance.
AUTHOR: Sauer B.
CORPORATE SOURCE: Du Pont-Merck Pharmaceut. Co., Experimental Station E328,Witmington, DE 19880-0328, United States
SOURCE: Journal of Molecular Biology, (1992) 223/4 (911-928). ISSN: 0022-2836 CODEN: JMOBAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The **Cre** recombinase efficiently causes site-specific DNA recombination at loxP sites placed into the eukaryotic genome. Since the loxP site of phage P1 is 34 base-pairs in size, the natural occurrence of this exact sequence is unlikely in any eukaryotic genome. However, related sequences may exist in eukaryotic genomes that could recombine at

low
efficiency with an authentic loxP site. This work identifies such cryptic lox sites in the yeast genome using a positive selection procedure that allows the detection of events occuring at a frequency of < 1 x 10-7. The selection is based on the disruption/reconstruction of the yeast gene YGL022. Disruption of YGL022 confers multiple drug sensitivity. Recombination events at a loxP site 5' to the structural gene restore expression of YGL022 and result in a multiple drug resistant phenotype. These drug resistant mutants all display chromosomal rearrangements resulting from low-frequency Cre-mediated recombination with an endogenous cryptic lox site. Ten such sites have been found and they have been mapped physically to a number of different yeast chromosomes. Although the efficiency of Cre-mediated recombination between loxP and such endogenous sites is quite low, it may be possible to redesign recombination substrates to improve recombination efficiency. Because of the greater complexity of the human and mouse genomes compared with yeast an analogous situation is likely to exist in these organisms. The availability of such sites would be quite useful in the development of alternative strategies for gene therapy and in the generation of transgenic animals.

=> d his

(FILE 'HOME' ENTERED AT 09:18:04 ON 08 JUN 2001)

FILE 'EMBASE, BIOSIS, LIFESCI, MEDLINE, CAPLUS' ENTERED AT 09:18:45 ON 08 JUN 2001
L1 0 S CRE/LOXP
L2 11929 S CRE
L3 160055 S TRANSGEN?
L4 1391 S L2 AND L3
L5 61 S L4 AND (GENE THERAPY)
L6 38 DUP REM L5 (23 DUPLICATES REMOVED)

=> s l4 and tACE
L7 0 L4 AND TACE

=> s l4 and angiotensin
L8 24 L4 AND ANGIOTENSIN

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9 9 DUP REM L8 (15 DUPLICATES REMOVED)

=> d l9 1-9 ibib abs

L9 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:350740 CAPLUS
DOCUMENT NUMBER: 131:14860
TITLE: Nucleic acids involved in the murine T/t-complex Responder phenotype and their diagnostic and therapeutic applications
INVENTOR(S): Herrmann, Bernhard; Koschorz, Birgit; Kispert, Andreas
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Forderung der Wissenschaften E.V., Germany
SOURCE: PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925815	A2	19990527	WO 1998-EP7395	19981118
WO 9925815	A3	19990819		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9916711	A1	19990607	AU 1999-16711	19981118
EP 1032595	A2	20000906	EP 1998-961219	19981118

R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE
PRIORITY APPLN. INFO.: EP 1997-120190 A 19971118
EP 1998-103596 A 19980302
WO 1998-EP7395 W 19981118

AB The present invention relates to nucleic acid mols. encoding expression products involved in the Responder function, which contributes to the phenomenon of transmission ratio distortion. The present invention also relates to regulatory regions of the genes corresponding to said nucleic acid mols. The mouse T/t-complex, a region of .apprx.12 cM genetic distance on the proximal part of chromosome 17, contains several loci acting in concert to produce a phenomenon called transmission ration distortion, indicating the fact that the so-called t-haplotype form of this chromosomal region has a selective advantage over the wild type form in that it is transmitted to the offspring at non-Mendelian ratios of up to 99%. The cDNA sequences of T66Bk mols. contain MARK2 kinase and rsk3 kinase homol. regions; T66Bk-2 cDNA contains only the MARK kinase homol. region, T66k-8 cDNA contains the complete sequence of T66Bk-2 except for a single base deleted resulting in a frameshift, T66k-7 cDNA corresponds to an antisense transcript of a T66Bk family member, and T66k-20 shows a strong similarity to the above members of the T66Bk gene family. Addnl. variants of the T66k family are shown from various mouse strains. The Responder function is located in the T66B region, is expressed in testis, and is expressed during spermatogenesis. Thus, the t-Responder may act as a component of a signaling cascade involved in sperm motility and/or the fertilization of oocytes and relates to methods of influencing transmission ratio. The present invention further relates to recombinant DNA mols. and vectors comprising said nucleic acid mols. and/or regulatory regions as well as to host cells transformed therewith. Addnl., the present invention relates to transgenic animals, comprising said nucleic acid mols., recombinant DNA mols. or vectors stably integrated into their genome. The various embodiments of the invention have a significant impact on breeding strategies by allowing for the specific selection of genetic traits and in particular of sex. Further, the present invention finds apptications in the development of contraceptives.

L9 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:166721 CAPLUS
DOCUMENT NUMBER: 130:205932
TITLE: Site-specific recombination in eukaryotes and useful constructs
INVENTOR(S): O'Gorman, Stephen; Wahl, Geoffrey
PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9910488	A1	19990304	WO 1998-US17852	19980828

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9892090	A1	19990316	AU 1998-92090	19980828

PRIORITY APPLN. INFO.: US 1997-919501 19970828
WO 1998-US17852 19980828

AB Site-specific recombinases provide a means of efficiently manipulating chromosomal sequences in mammalian cells in culture. Five lines of transgenic mice contg. a fusion gene encoding the mouse protamine 1 gene promoter and the Cre recombinase gene, ProCre, showed high levels of Cre-mediated recombination in the germline, but did not show appreciable recombination in other tissues. In other transgenic mice contg. a Cre targeting construct and the ProCre construct, between 80-100% of the progeny inherited the Cre -recombined target. When ES cells from the ProCre line were

transfected
with vectors contg. a loxP targeting construct, clones in which the loxP sites remained functional were readily isolated. These data establish that ProCre nucleic acid constructs will facilitate the prodn. of subtle, conditional or tissue-specific mutations in mice as well as the prodn. and anal. of mice with recombinase-conditional lethal alleles.
REFERENCE COUNT: 11
REFERENCE(S): (1) Aladjem, M; Molecular and Cellular Biology 1997, V17(2), P857 CAPLUS
(2) Dale, E; Proc Natl Acad Sci USA 1991, V88(23), P10558 CAPLUS
(3) Eyal, Y; Plant Cell 1995, V7, P373 CAPLUS
(4) Onouchi, H; Mol Gen Genet 1995, V247(6), P653 CAPLUS
(6) O'Gorman, S; Proc Natl Acad Sci USA 1997, V94(26), P14602 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 1999261684 EMBASE
TITLE: Efficient liver-specific deletion of a floxed human angiotensinogen transgene by adenoviral delivery of Cre recombinase in vivo.
AUTHOR: Stec D.E.; Davisson R.L.; Haskell R.E.; Davidson B.L.; Sigmund C.D.
CORPORATE SOURCE: C.D. Sigmund, Int. Med./Physiol./Biophysics Dept., 2191 Medical Laboratory, Univ. of Iowa Coll. of Medicine, Iowa City, IA 52242, United States. curt-sigmund@uiowa.edu
SOURCE: Journal of Biological Chemistry, (23 Jul 1999) 274/30 (21285-21290).
Refs: 40
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Tissue-specific ablation of gene function is possible in vivo by the Cre-loxP recombinase system. We generated transgenic mice containing a human angiotensinogen gene flanked by loxP sites (hAGT(floxn)). To examine the physiologic consequences of tissue-specific loss of angiotensinogen gene function in vivo, we constructed an adenovirus expressing Cre recombinase. Studies were performed in several independent lines of hAGT(flox) mice before and after intravenous administration of either Adcre or Ad.beta.Gal as a control. Systemic administration of Adcre caused a significant decrease in circulating human angiotensinogen and markedly blunted the pressor response to administration of purified recombinant human renin. Southern blot analysis of genomic DNA from various organs revealed that the Cre -mediated deletion was liver-specific. Further analysis revealed the absence of full-length human angiotensinogen mRNA and protein in the liver but not the kidney of Adcre mice, consistent with the liver being the target for adenoviruses administered intravenously. These studies demonstrate that extra-hepatic sources of angiotensinogen do not contribute significantly to the circulating pool of angiotensinogen and provide proof-of-principle that the Cre-loxP system can be used effectively to examine the contribution of the systemic and tissue renin-angiotensin system to normal and pathological regulation of blood pressure.

L9 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:667362 CAPLUS
DOCUMENT NUMBER: 131:349439
TITLE: Regulation of GATA-4 and AP-1 in transgenic mice overexpressing cardiac calsequestrin
AUTHOR(S): Suzuki, Y. J.; Ikeda, T.; Shi, S. S.; Kitta, K.; Kobayashi, Y. M.; Morad, M.; Jones, L. R.; Blumberg, J. B.
CORPORATE SOURCE: Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, 02111, USA
SOURCE: Cell Calcium (1999), 25(6), 401-407
CODEN: CECADV; ISSN: 0143-4160
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Transgenic mouse hearts overexpressing the Ca2+-binding protein calsequestrin (CSQ) have an accompanying 10-fold increase in the sarcoplasmic reticulum (SR) Ca2+ load, however, exhibits slow and small Ca2+-induced Ca2+ release. Such slow kinetics of Ca2+ release may have activated excitation-transcription coupling as CSQ overexpressing hearts have induced levels of NFAT and GATA-4 activities and higher levels of c-fos mRNA and cFos protein compared to those of non-transgenic littermates. Adaptive responses, however, appear to downregulate transcriptional regulators controlling c-fos gene including serum response factor and Ca2+/cAMP response element-binding protein. CSQ-overexpressing hearts also had decreased levels of cJun protein, resulting in downregulated AP-1 activity. The mRNA levels of angiotensin II type1a receptor which requires AP-1 and GATA-4 for gene transcription was suppressed in CSQ overexpressing hearts. These results demonstrate that CSQ can regulate GATA-4- and AP-1-dependent transcriptional events, indicating the existence of SR-nuclear circuits of signal transduction in adult cardiac muscle.
REFERENCE COUNT: 29
REFERENCE(S): (1) Bootman, M; Cell 1995, V83, P675 CAPLUS
(2) Bradford, M; Anal Biochem 1976, V72, P248 CAPLUS
(3) Dolmetsch, R; Nature 1997, V386, P855 CAPLUS
(4) Fried, M; Nucleic Acid Res 1981, V9, P6505 CAPLUS
(5) Garner, M; Nucleic Acid Res 1981, V9, P3047 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:287821 CAPLUS
DOCUMENT NUMBER: 129:37166
TITLE: A cyclic AMP response element in the angiotensin-converting enzyme gene and the transcription factor CREM are required for transcription of the mRNA for the testicular isoenzyme
AUTHOR(S): Kessler, Sean P.; Rowe, Theresa M.; Blendy, Julie A.; Erickson, Robert P.; Sen, Ganes C.
CORPORATE SOURCE: Department Molecular Biology, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, OH, 44195, USA
SOURCE: J. Biol. Chem. (1998), 273(16), 9971-9975
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The angiotensin-converting enzyme (ACE) gene produces two mRNA species from tissue-specific promoters. The transcription start site of the mRNA for the smaller testicular isoenzyme (ACET) is located within an intron of the larger transcription unit that encodes the pulmonary isoenzyme (ACEP). The authors have previously demonstrated that a 298-base pair DNA fragment, 5' to the rabbit ACET mRNA transcription initiation site, can activate the testicular expression of a transgenic reporter gene. In the current study, using the same transgenic reporter system, the authors identified a putative cAMP response element present within this DNA fragment to be absolutely essential for transcriptional activation. Moreover, the authors obsd. that ACET mRNA was not expressed in the testes of mice homozygous for a null mutation in the transcription factor CREM. However, in the same mice, ACEP mRNA was abundantly expressed in the lung. Our observations indicate that ACET mRNA expression in the testes is regulated by the putative cAMP response element present 5' to the transcription start site and the corresponding transcription factor CREM.

L9 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:499250 CAPLUS
DOCUMENT NUMBER: 127:172237
TITLE: Neuroendocrine cell lines for efficient synthesis and secretion of foreign proteins
INVENTOR(S): Newgard, Christopher B.; Halban, Philippe A.; Normington, Karl D.; Clark, Samuel A.; Thigpen, Anice E.; Quaade, Christian; Kruse, Fred; et al.
PATENT ASSIGNEE(S): Board of Regents, University of Texas System, USA; Betagene, Inc.; Newgard, Christopher B.; Halban, Philippe A.; Normington, Karl D.; Clark, Samuel A.; Thigpen, Anice E.
SOURCE: PCT Int. Appl., 278 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9726334	A1	19970724	WO 1997-US760	19970117

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 6087129	A	20000711	US 1996-589028	19960119
CA 2246268	AA	19970724	CA 1997-2246268	19970117
AU 9718309	A1	19970811	AU 1997-18309	19970117
EP 876484	A1	19981111	EP 1997-903838	19970117

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: US 1996-589028 A2 19960119
WO 1997-US760 W 19970117

AB Methods of constructing neuroendocrine cell lines capable of high-level expression of a foreign gene and efficient secretion of the gene product are described. Such a cell line has lost the ability to express a gene that encodes a major cell gene product specific to the cell line. The host cell machinery normally used to produce this polypeptide then becomes spare prodn. capacity for the synthesis of the foreign gene product. These lines or the gene products have a no. of therapeutic uses, e.g. in treatment of disease, in the development of vaccines. The gene may be expressed from a strong animal or animal virus promoter and preferably it is an analog of the major gene inactivated in the development, e.g. a human gene expressed in an insulinoma-derived line. This makes use of the endogenous accessory systems for post-translational modification and secretion of the gene product. Stable expression of the human insulin gene in rat insulinoma cells that have had the endogenous insulin gene insertionally inactivated is demonstrated. These cells also efficiently secreted human insulin and accurately processed the human proinsulin to insulin.

L9 ANSWER 7 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 97368207 EMBASE
DOCUMENT NUMBER: 1997368207
TITLE: Expression of testis **angiotensin**-converting enzyme is mediated by a cyclic AMP responsive element.
AUTHOR: Esther C.R. Jr.; Semeniuk D.; Marino E.M.; Zhou Y.; Overbeek P.A.; Bernstein K.E.
CORPORATE SOURCE: Dr. K.E. Bernstein, WMB, Deptartment of Pathology, Emory University, Atlanta, GA 30322, United States
SOURCE: Laboratory Investigation, (1997) 77/5 (483-488). Refs: 33 ISSN: 0023-6837 CODEN: LAINAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Testis **angiotensin**-converting enzyme (testis ACE), an ACE isozyme that plays an important role in male fertility, is transcribed from a unique promoter active only in developing spermatids. In vitro analysis suggests the importance of a cyclic AMP response element (CRE)-like region within the testis ACE promoter, and similar DNA motifs are important in the expression of a variety of testis-specific genes. In the present study, we examined the effects of mutations in the CRE-like element on testis ACE promoter activity in vivo using **transgenic** mice. Disruption of this element reduced reporter gene expression to near background levels. In contrast, conversion of the CRE-like element to a consensus CRE-binding site resulted in high level expression of the reporter gene specifically in the testis. These experiments prove that the CRE-like element is essential for testis ACE promoter activity, although it does not appear to be responsible for its tissue specificity. These data provide insight into how a phenotypically differentiated tissue, ie, male germ cells, regulate tissue-specific gene expression.

L9 ANSWER 8 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 96241517 EMBASE
DOCUMENT NUMBER: 1996241517
TITLE: Species variation in the testicular **angiotensin** converting enzyme promoter studied in **transgenic** mice.
AUTHOR: Erickson R.P.; Kessler S.; Kreming H.; Sen G.C.
CORPORATE SOURCE: Steele Memorial Children's Res. Ctr., College of Medicine, University of Arizona, 1501 N. Campbell Avenue,Tucson, AZ 85724, United States
SOURCE: Molecular Reproduction and Development, (1996) 44/3 (324-331). ISSN: 1040-452X CODEN: MREDEE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have studied the control of transcription of the testicular **angiotensin** converting enzyme (ACEt) in normal and **transgenic** mice. Northern analyses, including a developmental curve and separated germ cells, for ACEt mRNA suggest predominantly post-meiotic expression. Mice **transgenic** for a construct containing the proximal 298 bp of the rabbit ACEt promoter, with chloramphenicol acetyl transferase (CAT) as a recorder, showed correct tissue regulation while a 86 bp fragment of the promoter led to no expression. Many candidate transacting factor binding elements, previously identified as candidate regulators of transcription driving spermatogenesis, are scattered across this 298 bp in the rabbit (but not the mouse) promoter and may lead to tissue specificity. The recent finding that the proximal 91 bp of the mouse ACEt promoter leads to tissue specific expression of a recorder gene (Howard et al., 1993) emphasizes the difference between the two species and the importance of a cAMP response element (CRE) within this fragment for tissue specific expression. This CRE is conserved in the rabbit promoters we used.

L9 ANSWER 9 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
ACCESSION NUMBER: 93006878 EMBASE
DOCUMENT NUMBER: 1993006878
TITLE: Sperm-specific expression of **angiotensin** -converting enzyme (ACE) is mediated by a 91-base-pair promoter containing a CRE-like element.
AUTHOR: Howard T.; Balbgh R.; Overbeek P.; Bernstein K.E.
CORPORATE SOURCE: Department of Pathology, Emory University,Atlanta, GA 30322, United States
SOURCE: Molecular and Cellular Biology, (1993) 13/1 (18-27). ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The gene encoding the testis isozyme of **angiotensin**-converting enzyme (testis ACE) is one example of the many genes expressed uniquely during spermatogenesis. This protein is expressed by developing germ cells late in their development and results from the activation of a sperm-specific promoter that is located within intron 12 of the gene encoding the somatic isozyme of ACE. In vitro transcription, DNase footprinting, gel shift assays, and **transgenic** mouse studies have been used to define the minimal testes ACE promoter and to characterize DNA-protein interactions mediating germ cell- specific expression. These studies show that proper cell- and stage-specific expression of testis ACE requires only a small portion of the immediate upstream sequence extending to -91. A critical motif within this core promoter is a cyclic AMP-responsive element sequence that interacts with a testis-specific transactivating factor. Since this putative cyclic AMP-responsive element has been conserved within the testis ACE promoters of different species and is found at the same site in other genes that are expressed specifically in the testis, it may provide a common mechanism for the recognition of sperm-specific promoters.

=> s thomas k?/au
L10 3992 THOMAS K?/AU

=> d his

(FILE 'HOME' ENTERED AT 09:18:04 ON 08 JUN 2001)

FILE 'EMBASE, BIOSIS, LIFESCI, MEDLINE, CAPLUS' ENTERED AT 09:18:45 ON 08
JUN 2001
L1 0 S CRE/LOXP
L2 11929 S CRE
L3 160055 S TRANSGEN?
L4 1391 S L2 AND L3
L5 61 S L4 AND (GENE THERAPY)
L6 38 DUP REM L5 (23 DUPLICATES REMOVED)
L7 0 S L4 AND TACE
L8 24 S L4 AND ANGIOTENSIN
L9 9 DUP REM L8 (15 DUPLICATES REMOVED)
L10 3992 S THOMAS K?/AU

=> s l10 and l4
L11 1 L10 AND L4

=> d l11 ibib abs

L11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CAPLUS
DOCUMENT NUMBER: 134:81749
TITLE: Method for deleting a nucleic acid sequence in a specified tissue from a DNA introduced into the organism
INVENTOR(S): **Thomas, Kirk R.**; Bernstein, Kenneth E.; Bunting, Michaeline; Greer, Joy; Capecchi, Mario
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000809	A1	20010104	WO 2000-US17828	20000629

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-141267 P 19990630
AB The present invention is directed to a method for deleting DNA sequences in a tissue specific manner. In one embodiment, DNA sequences are specifically deleted in germline tissue. In a second embodiment, DNA sequences are specifically deleted in desired somatic tissue. The present invention is further directed to a nucleic acid mol. for use in the method. More specifically, a nucleic acid mol. is provided by the present invention which comprises (a) a recombinase site, (b) a tissue-specific promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a recombinase site. The nucleic acid mol. may further comprise a gene which is desired to be incorporated into and expressed in a **transgenic** organism. The method can be used in both plants and animals, and has many applications as described herein.
REFERENCE COUNT: 1
REFERENCE(S): (1) Kitamoto; Biochemical and Biophysical Research Communications 1996, V222(3), P742 CAPLUS

=> s bernstein k?/ai
'AI' IS NOT A VALID FIELD CODE
'AI' IS NOT A VALID FIELD CODE
'AI' IS NOT A VALID FIELD CODE
'AI' IS NOT A VALID FIELD CODE
'AI' IS NOT A VALID FIELD CODE
L12 0 BERNSTEIN K?/AI

=> s bernstein k?/au
L13 695 BERNSTEIN K?/AU

=> s l13 and l4
L14 10 L13 AND L4

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15 3 DUP REM L14 (7 DUPLICATES REMOVED)

=> d l15 1-3 ibib abs

L15 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CAPLUS
DOCUMENT NUMBER: 134:81749
TITLE: Method for deleting a nucleic acid sequence in a specified tissue from a DNA introduced into the organism
INVENTOR(S): Thomas, Kirk R.; **Bernstein, Kenneth E.**; Bunting, Michaeline; Greer, Joy; Capecchi, Mario
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000809	A1	20010104	WO 2000-US17828	20000629

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-141267 P 19990630
AB The present invention is directed to a method for deleting DNA sequences in a tissue specific manner. In one embodiment, DNA sequences are specifically deleted in germline tissue. In a second embodiment, DNA sequences are specifically deleted in desired somatic tissue. The present invention is further directed to a nucleic acid mol. for use in the method. More specifically, a nucleic acid mol. is provided by the present invention which comprises (a) a recombinase site, (b) a tissue-specific promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a recombinase site. The nucleic acid mol. may further comprise a gene which is desired to be incorporated into and expressed in a **transgenic** organism. The method can be used in both plants and animals, and has many applications as described herein.
REFERENCE COUNT: 1
REFERENCE(S): (1) Kitamoto; Biochemical and Biophysical Research Communications 1996, V222(3), P742 CAPLUS

L15 ANSWER 2 OF 3 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 97368207 EMBASE
DOCUMENT NUMBER: 1997368207
TITLE: Expression of testis angiotensin-converting enzyme is mediated by a cyclic AMP responsive element.
AUTHOR: Esther C.R. Jr.; Semeniuk D.; Marino E.M.; Zhou Y.; Overbeek P.A.; **Bernstein K.E.**
CORPORATE SOURCE: Dr. K.E. Bernstein, WMB, Deptartment of Pathology, Emory University, Atlanta, GA 30322, United States
SOURCE: Laboratory Investigation, (1997) 77/5 (483-488).
Refs: 33
ISSN: 0023-6837 CODEN: LAINAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology

LANGUAGE: English
SUMMARY LANGUAGE: English
AB Testis angiotensin-converting enzyme (testis ACE), an ACE isozyme that
plays an important role in male fertility, is transcribed from a unique promoter active only in developing spermatids. In vitro analysis suggests
the importance of a cyclic AMP response element (CRE)-like region within the testis ACE promoter, and similar DNA motifs are important in the expression of a variety of testis-specific genes. In the present study, we examined the effects of mutations in the CRE -like element on testis ACE promoter activity in vive using **transgenic** mice. Disruption of this element reduced reporter gene expression to near background levels. In contrast, conversion of the **CRE-like** element to a consensus **CRE**-binding site resulted in high level expression of the reporter gene specifically in the testis. These experiments prove that the **CRE**-like element is essential for testis ACE promoter activity, although it does not appear to be responsible for its tissue specificity. These data provide insight into how a phenotypically differentiated tissue, ie, male gem cells, regulate tissue-specific gene expression.

L15 ANSWER 3 OF 3 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 93006878 EMBASE
DOCUMENT NUMBER: 1993006878
TITLE: Sperm-specific expression of angiotensin-converting enzyme
(ACE) is mediated by a 91-base-pair promoter containing a **CRE**-like element.
AUTHOR: Howard T.; Balbgh R.; Overbeek P.; **Bernstein K.E.**
CORPORATE SOURCE: Department of Pathobgy, Emory University,Atlanta, GA
30322, United States
SOURCE: Molecular and Cellular Biology, (1993) 13/1 (18-27).
ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The gene encoding the testis isozyme of angiotensin-converting enzyme
(testis ACE) is one example of the many genes expressed uniquely during
spermatogenesis. This protein is expressed by developing germ cells late
in their development and results from the activation of a sperm-specific promoter that is located within intron 12 of the gene encoding the somatic
isozyme of ACE. In vitro transcription, DNase footprinting, gel shift assays, and **transgenic** mouse studies have been used to define the minimal testes ACE promoter and to characterize DNA-protein interactions mediating germ cell- specific expression. These studies show
that proper cell- and stage-specific expression of testis ACE requires only a small portion of the immediate upstream sequence extending to -91.
A critical motif within this core promoter is a cyclic AMP-responsive element sequence that interacts with a testis-specific transactivating factor. Since this putative cyclic AMP- responsive element has been conserved within the testis ACE promoters of different species and is found at the same site in other genes that are expressed specifically in the testis, it may provide a common mechanism for the recognition of sperm-specific promoters.

=> s bunting m?/au
L16 85 BUNTING M?/AU

=> s l16 and l4
L17 1 L16 AND L4

=> d l17 ibib abs

L17 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CAPLUS
DOCUMENT NUMBER: 134:81749
TITLE: Method for deleting a nucleic acid sequence in a specified tissue from a DNA introduced into the organism
INVENTOR(S): Thomas, Kirk R.; Bernstein, Kenneth E.; **Bunting, Michaeline**; Greer, Joy; Capecchi, Mario
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000809	A1	20010104	WO 2000-US17828	20000629

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-141267 P 19990630
AB The present invention is directed to a method for deleting DNA sequences
in a tissue specific manner. In one embodiment, DNA sequences are specifically deleted in germline tissue. In a second embodiment, DNA sequences are specifically deleted in desired somatic tissue. The present
invention is further directed to a nucleic acid mol. for use in the method. More specifically, a nucleic acid mol. is provided by the present
invention which comprises (a) a recombinase site, (b) a tissue-specific promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a recombinase
site. The nucleic acid mol. may further comprise a gene which is desired
to be incorporated into and expressed in a **transgenic** organism. The method can be used in both plants and animals, and has many applications as described herein.
REFERENCE COUNT: 1
REFERENCE(S): (1) Kitamoto; Biochemical and Biophysical Research
Communications 1996, V222(3), P742 CAPLUS

=> s greer j/au
L18 292 GREER J/AU

=> s l18 and l4
L19 0 L18 AND L4

=> s l18 and loxp
L20 0 L18 AND LOXP

=> s capecchi m?/au
L21 449 CAPECCHI M?/AU

=> s l21 and l4
L22 7 L21 AND L4

=> dup rem l22
PROCESSING COMPLETED FOR L22
L23 3 DUP REM L22 (4 DUPLICATES REMOVED)

=> d l23 1-3 ibib abs

L23 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CAPLUS
DOCUMENT NUMBER: 134:81749
TITLE: Method for deleting a nucleic acid sequence in a specified tissue from a DNA introduced into the organism
INVENTOR(S): Thomas, Kirk R.; Bernstein, Kenneth E.; Bunting, Michaeline; Greer, Joy; **Capecchi, Mario**
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000809	A1	20010104	WO 2000-US17828	20000629

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-141267 P 19990630
AB The present invention is directed to a method for deleting DNA sequences
in a tissue specific manner. In one embodiment, DNA sequences are specifically deleted in germline tissue. In a second embodiment, DNA sequences are specifically deleted in desired somatic tissue. The present
invention is further directed to a nucleic acid mol. for use in the method. More specifically, a nucleic acid mol. is provided by the present
invention which comprises (a) a recombinase site, (b) a tissue-specific promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a recombinase
site. The nucleic acid mol. may further comprise a gene which is desired
to be incorporated into and expressed in a **transgenic** organism. The method can be used in both plants and animals, and has many applications as described herein.
REFERENCE COUNT: 1
REFERENCE(S): (1) Kitamoto; Biochemical and Biophysical Research
Communications 1996, V222(3), P742 CAPLUS

L23 ANSWER 2 OF 3 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2000433813 EMBASE
TITLE: Illegitimate **Cre**-dependent chromosome rearrangements in **transgenic** mouse spermatids.
AUTHOR: Schmidt E.E.; Taylor D.S.; Prigge J.R.; Barnett S.; **Capecchi M.R.**
CORPORATE SOURCE: M.R. Capecchi, Howard Hughes Medical Institute, University
of Utah, 15 North 2030 East, Salt Lake City, UT 84112-5331, United States. mario.capecchi@genetics.utah.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (5 Dec 2000) 97/25 (13702-13707). Refs: 45
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The bacteriophage P1 **Cre**/loxP system has become a powerful tool for in vivo manipulation of the genomes of **transgenic** mice. Although in vitro studies have shown that **Cre** can catalyze recombination between cryptic 'pseudo-xP' sites in mammalian genomes, to
date there have been no reports of loxP-site infidelity in **transgenic** animals. We produced lines of **transgenic** mice that use the mouse Protamine 1 (Prm1) gene promoter to express **Cre** recombinase in postmeiotic spermatids. All male founders and all **Cre**-bearing male descendents of female founders were sterile; females were unaffected. Sperm counts, sperm motility, and sperm morphology were normal, as was the mating behavior of the **transgenic** males and the production of two-celled embryos after mating. Mice that expressed similar levels of a derivative **transgene** that carries an inactive **Cre** exhibited normal male fertility. Analyses of embryos from matings between sterile **Cre**-expressing males and wild-type females indicared that **Cre**-catalyzed chromosome rearrangements in the spermatids that lead to abortive pregnancies with 100% penetrance. Similar **Cre**-mediated, but loxP-independent, genomic alterations may also occur in somatic tissues that express **Cre**, but, because of the greater difficulty of assessing deleterious effects of somatic mutations, these may go undetected. This study indicates that, following the use of the **Cre**/loxP site-specific recombination systems in vivo, it is prudent to eliminate or inactivate the **Cre** recombinase gene as rapidly as possible.

L23 ANSWER 3 OF 3 MEDLINE
ACCESSION NUMBER: 2000129922 MEDLINE
DOCUMENT NUMBER: 20129922 PubMed ID: 10662638
TITLE: Normal limb development in conditional mutants of Fgf4.
AUTHOR: Moon A M; Boulet A M; **Capecchi M R**
CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Human
Genetics, University of Utah School of Medicine, Salt Lake City, UT 84112, USA.
SOURCE: DEVELOPMENT, (2000 Mar) 127 (5) 989-96.
Journal code: ECW; 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403
AB Fibroblast growth factors (FGFs) mediate multiple developmental signals in
vertebrates. Several of these factors are expressed in limb bud structures
that direct patterning of the limb. FGF4 is produced in the apical ectodermal ridge (AER) where it is hypothesized to provide mitogenic and
morphogenic signals to the underlying mesenchyme that regulate normal limb
development. Mutation of this gene in the germline of mice results in early embryonic lethality, preventing subsequent evaluation of Fgf4 function in the AER. A conditional mutant of Fgf4, based on site-specific **Cre**/loxP-mediated excision of the gene, allowed us to bypass embryonic lethality and directly test the role of FGF4 during limb development in living murine embryos. This conditional mutation was designed so that concomitant with inactivation of the Fgf4 gene by excision of all Fgf4-coding sequences, a reporter gene was activated in Fgf4-expressing cells, allowing assessment of the site-specific recombination reaction. Although a large body of evidence led us to predict that ablation of Fgf4 gene function in the AER of developing mice
would result in abnormal limb outgrowth and patterning, we found that Fgf4
conditional mutants had normal limbs. Furthermore, expression patterns of
Shh, Bmp2, Fgf8 and Fgf10 were normal in the limb buds of the conditional
mutants. These findings indicate that the previously proposed FGF4-SHH
feedback loop is not essential for coordination of murine limb outgrowth and patterning. We suggest that some of the roles currently attributed to FGF4 during early vertebrate limb development may be performed by other
AER factors in vivo.

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FILE 'EMBASE, BIOSIS, LIFESCI, MEDLINE, CAPLUS' ENTERED AT 09:18:45 ON 08
JUN 2001
L1 0 S CRE/LOXP
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L4 1391 S L2 AND L3
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L7 0 S L4 AND TACE
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L10 3992 S THOMAS K?/AU
L11 1 S L10 AND L4
L12 0 S BERNSTEIN K?/AI
L13 695 S BERNSTEIN K?/AU
L14 10 S L13 AND L4
L15 3 DUP REM L14 (7 DUPLICATES REMOVED)
L16 85 S BUNTING M?/AU
L17 1 S L16 AND L4
L18 292 S GREER J/AU
L19 0 S L18 AND L4
L20 0 S L18 AND LOXP
L21 449 S CAPECCHI M?/AU
L22 7 S L21 AND L4
L23 3 DUP REM L22 (4 DUPLICATES REMOVED)

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Executing the logoff script...

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	SESSION	TOTAL
FULL ESTIMATED COST		127.42	127.57

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	SESSION	TOTAL
CA SUBSCRIBER PRICE		-16.46	-16.46

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